REMARKS

Specification

The Examiner contends that SEQ ID NO:18 and 19 constitute new matter. The Examiner contends that the specification does not explicitly contemplate a genus comprising SEQ ID NO:18 (Y_{16}NYAGG) or comprising SEQ ID NO:19 (TTCTTTTTTTCTCTTCNYAGG), and does not contemplate any species within the genus other than OPTIVS8. Applicant respectfully traverses.

Applicant submits that the present invention teaches a recombinant intron comprising particular unique combinations of 5' splice site, branch point, and 3'splice sites. The specification teaches a 5' splice site chosen to be exactly complementary to the 5' end of U1 snRNA (page 32, lines 15-18), whereas the branch point is chosen to maximize interaction with U2 snRNA and to match branch point sequence known to be obligatory for pre-mRNA splicing in yeast (page 32, line 27 to page 33, line 3). *See also* page 29, lines 1-12. The specification, however, does not teach a 3' splice site as a particular chosen sequence as evidenced at a minimum by the fact that two specific working embodiments are disclosed, one having the 3' splice sequence of OPTIVS8 TTCTTTTTTTCTCTTCACAGG 3'- as well as the weakened 3' splice sequence of TTCTTTAAATCTCTTCACAGG 3', which in fact disrupts the 16 pyrimidine tract. *See* page 39, lines 1 – 6 ([0110] of the published application).

Instead the specification teaches that:

(i) the consensus sequence for 3' splice site is Y_{11}NYAGG,

(ii) the polypyrimidine tract Y_{11} is the major determinant of splice site strength, and

(iii) optimal splicing requires at least 5 consecutive T residues in the polypyrimidine tract (page 33, lines 13-17, 22-24).

Accordingly, the present invention teaches a unique combination of 5' splice site and branch point, each having defined sequence, together with a 3' splice site that is conceptually defined by essential novel parameters wherein the 3' splice site matches the consensus sequence but extends the consensus polypyrimidine tract Y_{11} to a 16-base polypyrimidine tract, which in addition has 7 consecutive T residues (page 33, lines 18-20; *see also* page 29, lines 8-10). Hence, the model 3' splice site necessarily becomes Y_{16}NYAGG (SEQ ID NO:18), wherein the

Y_{16} tract contains 7 consecutive T residues. OPTIVS8 is given as an exemplary embodiment and is stated to be the same (page 31, line 29 to page 32, line 1).

Referring to page 31, line 29, ([0090] of the published application), the specification defines OPTIVS8 explicitly as an "exemplary synthetic intron." The specification on page 29, lines 1 – 16 ([0080] of the published application), clearly defines the synthetic intron in generic terms as follows:

Intron	5' splice site sequence matches consensus. 5' splice site sequence is exactly complementary to 5' end of U1 snRNA. Branch point sequence matches consensus. Branch point sequence is complementary to U2 snRNA. 3' splice site matches consensus. Polypyrimidine tract is 16 bases in length and contains 7 consecutive T's. (The tract preferably contains at least 5 consecutive T's.) Contains internal restriction enzyme sites . . .

Hence, Applicant submits that SEQ ID NO:18, with 7 consecutive T residues in the Y_{16} tract, is explicitly and/or implicitly supported in the originally filed specification. One of ordinary skill in the art would readily recognize that the present specification is explicitly and/or implicitly teaching a model 3' splice site Y_{16}NYAGG (SEQ ID NO:18), with 7 consecutive T residues in the Y_{16} tract. The Examiner has parsed the passage "For optimal splice function in OPTIVS8[B], the length of the polypyrimidine tract was extended to 16 bases, and its sequence was adjusted to contain 7 consecutive T residues" (paragraph [0093] of the published application), in arriving at a conclusion that the Applicant never contemplated a genera of 3' splice sites characterized by the sequence "Y_{16}NYAGG (SEQ ID NO:18), with 7 consecutive T residues in the Y_{16} tract." Applicant respectfully but strongly urges that this is an impermissibly narrow reading of the relevant passage and that Examiner has essentially imposed a requirement for verbatim support that finds no foundation in patent law. In so doing, the Examiner has impermissibly limited the scope of permissible claims to one exemplary embodiment, that of OPTIVS8.

Applicant submits herein that SEQ ID NO:18, including as containing 7 consecutive T residues in the Y_{16} tract is taught by the specification. Accordingly, Applicant respectfully requests that the objection of SEQ ID NO:18 under 35 U.S.C. §132 be withdrawn.

While explicitly disagreeing with the Examiner's characterization of SEQ ID NO:19 as new matter, SEQ ID NO:19 has been cancelled merely in the interests of advancing prosecution.

Rejection Under 35 U.S.C. §112

Claims 5, 10, 14, 51-54, 65-71 and 73-76 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

The Examiner indicates that amending the claims to recite "the sequence of" instead of "a sequence of" would obviate the rejection. Accordingly, claims 5, 10, 14 and 51 have been amended to recite "the sequence of." Consequently, Applicant respectfully requests that the rejection of claims 5, 10, 14 (and their dependent claims) be withdrawn.

Regarding claims 52-53, claim 52 is drawn to a plasmid of claim 10, wherein the 3' splice site is weakened with respect to the alternative 3' splice site. Claim 53 is drawn to a plasmid of claim 10 comprising CTTTTTTTC, wherein the 3' splice site is weakened with respect to the alternative 3' splice site by changing three consecutive T's to A's. Support for the claims can be found at page 39, lines 1-6:

> . . . the relative strength of the first 3' splice site was weakened by site-directed mutagenesis to change three consecutive T's to A's. Thus, in the sequence shown above for the OPTIVS8 intron, the included sequence 5'-CTTTTTTTC-3' was changed to 5'-CTTTAAATC-3'.

Thus, the specification broadly teaches weakening the first 3' splice site by changing three consecutive T's to A's. In one embodiment, the sequence CTTTTTTTC-3' was changed to 5'-CTTTAAATC-3'. The specification, however, does not teach CTTTAAATC as the only change that can be made. The OPTIVS8 intron is an exemplary intron and the specification only uses CTTTAAATC as an example of changing three consecutive T's to A's. In view of the teaching that a 3' splice site can be weakened by site-directed mutagenesis to change three consecutive T's to A's, one of ordinary skill in the art would readily recognize that any 3

consecutive T's can be changed to 3 A's in the sequence of CTTTTTTTC. Hence, Applicant submits that the subject matter of claims 52 and 53 has been described and supported in the specification explicitly or implicitly, thus satisfying the written description requirement.

Claim 65 has been amended to recite an intron comprising a 3' splice site having the sequence of Y_{16}NYAGG (SEQ ID NO:18), wherein Y_{16} contains 7 consecutive T residues. As discussed above, Applicant submits that the instant specification teaches a 3' splice site sequence Y_{16}NYAGG, wherein Y_{16} contains 7 consecutive T residues. Accordingly, Applicant submits that claim 65 as amended is fully supported by the originally filed specification, and no new matter has been added.

Cancelled claim 67 was rejected for reciting SEQ ID NO:19. As indicated above, SEQ ID NO:19 has been canceled merely for the sake of advancing the prosecution. This claim 67 has been corresponding cancelled while not in anyway acquiescing to the Examiner's objections to SEQ ID 19.

Claims 70 and 75 recite a branch point is located 24 to 38 nucleotides upstream from a site of splicing in the 3' splice site. Claims 71 and 73 recite a synthetic intron from about 90 to about 200 nucleotides in length. The Examiner contends that the specification only supports a synthetic intron with a size of 118 nucleotides, and the specification does not support a branch point being located within 24-38 nucleotides upstream of a 3' splice site. Applicant respectfully traverses.

The specification discloses a synthetic intron OPTIVS8 having 118 nucleotides and a branch point located 24 nucleotides upstream of a 3' splice site. However, as discussed above, the specification explicitly states that OPTIVS8 is only an exemplary synthetic intron. The present invention is not limited to this particular embodiment. The specification teaches a branch point is typically 18-38 nucleotides upstream of the 3' splice site, and the distance between the branch point and the 3' splice site in OPTIVS8 (24 nucleotides) falls within this range ([0092] of the published application). The specification also teaches most naturally occurring introns are 90-200 nucleotides in length, and the length of OPTIVS8 falls within this range ([0094] of the published application). Furthermore, the specification, at page 34, lines 17 – 19 ([0096] of the published app), states that "The 77 bases between the BbsI site and the

branch point sequence are random in sequence, except for the inclusion of the NheI restriction site." Clearly, the Applicant does not contemplate being limited to the specific irrelevant sequence between the 5' slice site and the branch point, although in a preferred embodiment, the generated synthetic intron has a total length of between 90 and 200, largely as a consequence of the length of the stretch between the 5' splice site and the branch point. In view of these teachings, Applicant strongly asserts that one of ordinary skill in the art would readily recognize that the specification is teaching explicitly or implicitly a synthetic intron can be 90-200 nucleotides in length and can have a branch point located 18-38 or 24-38 nucleotides upstream of the 3' splice site. The subject matter of claims 70-71, 73, and 75 are clearly taught and supported by the specification. For the sake of advancing the prosecution, however, claims 70-71, 73, and 75 have been canceled.

Limitations to Specific Embodiments under Section 112

To the extent that any §112 rejections are retained after the present amendments and such rejections limit the scope of the claims to a specific working embodiment, the rejection is respectfully but vigorously traversed. The "written description" requirement serves both to satisfy the inventor's obligation to fully teach the knowledge upon which the claims are based, and to demonstrate that the patentee was in possession of the invention that is claimed. *See Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46 (Fed. Cir. 2000) (the purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification"). Thus, the policy premises of the patent grant are fulfilled where the inventor's technical/scientific advance is added to the body of knowledge in return for the grant of patent exclusivity. *See Capon v Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005).

In the present application, the inventors have disclosed a synthetic intron that comprises a unique combination of 5' splice site and branch point, each having defined sequence, together with a 3' splice site that is conceptually defined by essential novel parameters that are added to a consensus sequence. Thus, whereas a consensus 3' splice site has the sequence Y_{11}NYAGG and those with optimal splicing have at least 5 consecutive T residues in the polypyrimidine tract, the specification teaches a novel 3' splice site whereby a consensus sequence is modified by extending the polypyrimidine tract Y_{11} to a 16-base polypyrimidine tract, which, in addition, has

7 consecutive T residues. By the fact that the 3' splice site of the invention is based on a consensus sequence, it would be immediately apparent to one of skill in the art that it is the motif and not the specific sequence that is important and that, according to the teaching of the invention, the splicing strength of various 3' splice sites can be improved by extension of the polypyrimidine tract and the inclusion of 7 consecutive T residues. Also readily apparent to one of skill in the art, the specific location of the run of consecutive T residues within the polypyrimidine tract is not critical. This is exemplified at least by that art cited by the examiner that features runs of consecutive "T"s. The consecutive "T"s occur on the 5' end of the polypyrimidine tract with Dirks but the 3' end of Rautmann.

On the flip side, if the scope of the claims is limited to single working embodiment, required in satisfaction of the best mode requirement, the Application will not receive a scope of protection that is commensurate with the teaching that has been provided. It is certainly readily apparent to one of skill in the art that there are many permutations of Y_{16}NYAGG having 7 consecutive T residues in the polypyrimidine tract, and if the Applicant is limited to the specific sequence of the working embodiment OPTIVS8, infringement will be readily avoided while still realizing the benefits of the teaching. As with the maturation of related technologies, the written description requirement no longer requires an explicit description of every covered embodiment where sequences are involved. The present situation can be analogized to the issues facing the parties in the above referenced *Capon v Eshhar* case. As stated recently by the Federal Circuit:

> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Both Eshhar and Capon explain that this invention does not concern the discovery of gene function or structure, as in Lilly. The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

Capon v Eshhar, 418 F.3d at 1358.

As with Capon and Eshhar, the Examiner's apparent requirement for a listing of every possible permutation of the claimed sequence does not add descriptive substance. The consensus

sequence is known and a full description of how the sequence is to be modified has been given with a specificity that would be readily apparent to one of skill in the art. In view of the above remarks, Applicant respectfully requests that the rejection of claims 5, 10, 14, 51-54, 65, and 69 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of Claim 5 Under 35 U.S.C. §103

Claim 5 stands rejected under 35 U.S.C. §103(a) as being unpatentable over either Mascarenhas et al. (Plant Molecular Biology 15:913 (1990)) or Petitclerc et al. (J. Biotechnology 40:169 (1995)) in view of any one of Mulvihill et al. (U.S. Patent 5,648,254), Carrano et al. (U.S. Patent 5,739,118) or Ligon et al. (U.S. Patent 5,723,759). The rejection is respectfully traversed.

Claim 5 has been amended to recite a plasmid carrying a synthetic intron comprising a 5' splice site having the sequence of residues 1-9 of SEQ ID NO:13, a branch point having the sequence of residues 93-99 of SEQ ID NO:13, and a 3' splice site having the sequence of residues 102-122 of SEQ ID NO:13. The Examiner indicates that amending the claim to recite "the sequence of" instead of "a sequence of" would obviate the rejection. Accordingly, Applicant respectfully requests that the rejection of claim 5 under 35 U.S.C. §103(a) be withdrawn.

Rejection of Claims 10 and 51 Under 35 U.S.C. §103

Claim 10 stands rejected and claim 51 is newly rejected under 35 U.S.C. §103(a) as being unpatentable over Mascarenhas et al. (Plant Molecular Biology 15:913 (1990)) or Petitclerc et al. (J. Biotechnology 40:169 (1995)) in view of Mulvihill et al. (U.S. Patent 5,648,254), Carrano et al. (U.S. Patent 5,739,118) or Ligon et al. (U.S. Patent 5,723,759), and further in view of Zitvogel et al. (Human Gene Therapy 5:1493 (1994)). The rejection is respectfully traversed.

Claim 10 has been amended to recite a plasmid carrying an intron comprising a 5' splice site having the sequence of residues 1-9 of SEQ ID NO:13, a branch point having the sequence of residues 93-99 of SEQ ID NO:13, and a 3' splice site having the sequence of residues 102-122 of SEQ ID NO:13. Claim 51 has been amended to recite a 3' splice site having the sequence of residues 102-122 of SEQ ID NO:13. The Examiner indicates that amending the claims to recite "the sequence of" instead of "a sequence of" would obviate the rejection. Accordingly,

Applicant respectfully requests that the rejection of claims 10 and 51 under 35 U.S.C. §103(a) be withdrawn.

Rejection of Claim 14 Under 35 U.S.C. §103

Claim 14 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Dirks et al. (Gene 128:247 (1993)) in view of Rautmann and Breathnach (Nature 315:430 (1985)). The rejection is respectfully traversed.

Claim 14 as amended is drawn to a plasmid carrying a synthetic intron comprising a 5' splice site having the sequence of residues 1-9 of SEQ ID NO:13, a branch point having the sequence of residues 93-99 of SEQ ID NO:13, and a 3' splice site having the sequence of residues 102-122 of SEQ ID NO:13. The Examiner indicates that amending the claim to recite "the sequence of" instead of "a sequence of" would obviate the rejection. Accordingly, Applicant respectfully requests that the rejection of claim 14 under 35 U.S.C. §103(a) be withdrawn.

New Grounds of Rejection

Claims 65, 70, 71 and 73 are rejected under 35 U.S.C. §112, first paragraph, as containing new matter. This rejection is respectfully traversed.

Claim 65 has been amended to recite an intron comprising a 3' splice site having the sequence of Y_{16}NYAGG (SEQ ID NO:18), wherein Y_{16} contains 7 consecutive T residues. As discussed above, Applicant submits that claim 65 as amended is supported by the instant specification that explicitly and/or implicitly teaches a 3' splice site sequence Y_{16}NYAGG, wherein Y_{16} contains 7 consecutive T residues. Claims 70, 71 and 73 have been canceled. Hence, Applicant respectfully requests that the rejection of claim 65 under 35 U.S.C. §112, first paragraph, be withdrawn.

Respectfully submitted,

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